REMARKS / ARGUMENTS

1. No New Matter Has Been Added

No new matter has been introduced by way of this amendment. For each amendment made, proper support exists in the originally filed specification at the pages indicated.

2. Summary of Amendments

Claim 101 has been amended to specify that the extraction phase is "polymeric".

Dependent claim 102 has been amended to specify that the biocompatible protection layer is "polymeric"

Dependent claim 103 has been amended to remove the limitations relation to the extraction phase.

New dependent claims 120 and 121 have been added to recite the limitations regarding the extraction phase previously recited in claim 103.

New claim 120 recites that the extraction phase comprises "substituted or unsubstituted poly (dimethylsiloxane), polyacrylate, poly (ethylene glycol), carbon, poly(divinylbenzene) or polypyrrole".

New claim 121 stipulates that the extraction phase comprises "a bioaffinity agent selected from the group consisting of a selective cavity, a molecular recognition moiety, a molecularly imprinted polymer and an immobilized antibody".

No change has been made to claims 101, 104 - 107, 109, 118 or 119.

3. Support for Claim Amendments Within Specification

The limitation of "polymeric" with respect to the extraction phase recited in claim 101 is supported by the exemplary extraction phases recited in the previous version of claim 103, which are now found in new claim 120, as well as in the examples of the description, and in the passage provided below:

> The extraction phase itself may comprises any composition capable of

> binding a component of interest. It may, for example be a polymeric composition such as substituted or unsubstituted poly (dimethylsiloxane), polyacrylate, poly (ethylene glycol) or polypyrrole.
>
> (page 11, lines 23-27)

The limitation of "polymeric" with respect to the biocompatible protection layer recited in claim 102 is supported by the description in the passage provided below:

> The extraction phase is advantageously biocompatible, as necessary. Optionally, the fibre may be additionally at least partially coated with a biocompatible protection layer, which can surround the extraction phase. Such a biocompatible protection layer may comprise polypyrrole or derivatised cellulose, or any such polymer as would provide protection.
>
> (page 11, lines 18-22)

The limitation now found in claim 120, which depends from claim 101 is supported by passages in the description which do not require a biocompatible protection layer to be present. Pervious claim 103, which depended from claim 102 (and thus required the presence of the biocompatible protection layer) recited this limitation, and passages in the description also recite this limitation without requiring the presence of the protection layer. Specific passages are provided below:

> The extraction phase itself may comprises any composition capable of binding a component of interest. It may, for example be a polymeric composition such as substituted or unsubstituted poly (dimethylsiloxane), polyacrylate, poly (ethylene glycol) or polypyrrole.
>
> (page 11, lines 23-26)

> Polypyrrole itself has good biocompatibility. It has been used for several years in biosensor devices without any evidence of toxicity, immunogenesis (initiation of an immune response) or thrombogenesis (initiation of clotting response). It is an example of an extraction phase that is suitable for exposing directly to the investigated system.
>
> (page 22, lines 21-24)

> Satisfactory calibration curves were obtained for the very volatile compounds namely methanol, acetone, dichloromethane and chloroform when a 75-um carboxen™/ polydimethylsiloxane (CX/PDMS) fiber/coating was used.
>
> (page 45, lines 9 to 11)

The limitation now found in claim 121, which depends from claim 101 is supported by passages in the description which do not require a biocompatible protection layer to be present. Pervious claim 103, which depended from claim 102 (and thus required the presence

of the biocompatible protection layer) recited this limitation. Passages in the description also recite this limitation without requiring the presence of the protection layer. Specific passages are provided below:

> The extraction phase itself may comprises any composition capable of binding a component of interest. It may, for example be a polymeric composition such as substituted or unsubstituted poly (dimethylsiloxane), polyacrylate, poly (ethylene glycol) or polypyrrole. Alternatively, the extraction phase may have a bioaffinity agent on its surface, such as a selective cavity, a molecular recognition moiety, a molecularly imprinted polymer, or an immobilized antibody. The extraction phase may contain any of these in combination.
>
> (page 11, lines 23-29)

4. Claim Rejections - 35 USC §103

That Applicant believes that the claim rejections raised on pages 2 to 9 under 35 USC §103 are traversed by the amendments and arguments in support thereof put forward herein. Independent claim 101 should now be considered both novel and inventive. All dependent claims should thus also be considered novel and inventive. The amendment made to claims emphasize features not taught or suggested in any combination of prior art references.

The combined teachings of Pompidou et al. and Faxon et al. were applied against claim 101 in support of an obviousness rejection. However, these two references, either alone or in combination do not provide all of the components now recited in claim 101 to arrive at a device comparable to the device recited in claim 101. Not only do the combined teachings not suggest or motivate the reader to combine the respective teachings, or generally indicate that the references be modified to combine the teachings; but neither do the combined teachings provide a reasonable expectation of success, should the teachings be combined. Further, the combined teachings do not provide any suggestion that a combination be made that would be in any way comparable to the device of claim 101. Further, the art fields of Pompidou et al., and Faxon et al. are adequately disparate from each other, and remote from the field of the present invention, to the extent that they are inappropriate to combine. Emphasis is placed on claim 101 for initial purposes of this analysis, and dependent claims will be discussed below.

4.1. The Device of Pompidou et al. Does Not Include a Fiber, a Positioning Device or a Fiber Holding Region, as Asserted by the Examiner

Pompidou et al. reference relates to a device that can be inserted into a biological sample or system. A flexible rod is used to insert the device. At the terminal end of the flexible rod is attached a microsystem comprising a rigid support on which biological or chemical substances (such as antibodies) are arrayed. Distinctions between various components between which the Examiner has made comparisons are provided below. Other distinctions also exist, which are not focused on in this response, in the interests of brevity.

4.1.1. The Microsystem is Not Comparable to the Fiber

The examiner asserts on page 3 of the Action that the microsystem itself is the equivalent of a "fiber", and that the flexible rod is itself an equivalent of a "positioning device" recited in claim 101. The Applicant disagrees, and believes that the Examiner has misunderstood the invention as claimed in claim 101. In particular, the microsystem of Pompidou et al. does not meet the criteria set forth for the fiber in claim 101. Firstly, the fibre has a "coated end" coated with an "extraction phase" that is now stipulated as a "polymeric extraction phase". The microsystem does not have any coating thereon, but instead has an "array" of biological or chemical substances, which implies an orderly placement of such substances. There is no stipulation anywhere in Pompidou et al. that the array be formed of polymeric materials, or that the array is "coated" on the microsystem. Instead, orderly placement of antibodies, for example as depicted in Figure 6, and as implied through the term "array" is emphasized. The following passage emphasizes this distinction:

> The active layer surrounding the rigid support can be a flat ribbon or a round cord on which the reagents are deposited and fixed. It can involve ligands and, notably, antigens or antibodies, but also nucleotides.
>
> (Col. 2, lines 37-39)

There is no suggestion in Pompidou et al. that a "coated end" comprises, instead of an array of antibodies, a coating of a polymeric extraction phase. The Examiner's attention is drawing to the following passages of Pompidou et al., which indicate that the array of biomolecules is envisioned as a parallel to a "biochip", which requires very specific manufacturing conditions, and could not be compared to a coating at the end of a fibre:

> Investigation microsystems employing an array of biological molecules placed in given positions on a surface are described in the prior art. Those systems, known as "biochips" or DNA chips, are useful for the investigation of polynucleotide or amino acid sequences. Examples of such systems are described, for example, in the European patent applications published under No. 619,321, No. 373,203 and No. 691,978. Other investigation microsystems are, for example, the microanalysis tests using ligand/receptor type reactions or microimmunoanalyses using antigen/antibody type reactions.
>
> (col. 1, lines 13-23)

4.1.2 The Flexible Rod is Not Comparable to The Positioning Device

The Examiner asserts on page 3 of the action that the "flexible rod" taught by Pompidou et al. is the equivalent of the positioning device recited in claim 101. The applicant respectfully disagrees, as all features defining the positioning device in claim 101 are not found in the description of the flexible rod. The positioning device requires two components: a catheter, and a fiber holding region. The flexible rod itself can be not be described as the combined equivalent of a catheter and a fiber holding region. Claim 101 stipulates that the fiber *extends through the catheter.* However the microsystem is *fixed to the end of* the flexible rod, and thus it is not possible for the microsystem to "extend through" the flexible rod. Specific passages showing that the microsystem is *fixed to the end of* the flexible rod are provided below:

> Device for in situ analysis and/or treatment consisting of a flexible rod and micro system *fixed at one end of said flexible rod*
>
> (Title of Pompidou et al., with emphasis added)

> This objective is attained according to the present invention thanks to an apparatus for chemical or biological analysis or treatment in situ comprising (i) a microsystem for investigation of a substrate and/or for delivery of active agents in a substrate and (ii) a flexible rod *to one end of which the microsystem is attached* and the other end of which is intended for the control of said microsystem, and in that, in the case of an investigation, the microsystem is not of the type based on analysis of the emission and detection of a fluorescent signal.
>
> (col 1, lines 43-52, with emphasis added)

> This objective is attained according to the present invention thanks to an apparatus for chemical or biological analysis or treatment in situ comprising (i) a microsystem for investigation of a substrate and/or for delivery of active agents in a substrate and (ii) a flexible rod *to one end of which the microsystem is attached* and the other end of which is intended for the control of said microsystem,

> and in that, in the case of an investigation, the microsystem is not of the type based on analysis of the emission and detection of a fluorescent signal.
>
> (col 1, lines 43-52, with emphasis added)

It should now be clear to the examiner that the flexible rod is not the equivalent of or in any way comparable to the positioning device of claim 101 (having two components: a catheter and a fiber holding region) through which a fiber extends. There is no mention in Pompidou et al. that a component of any type could extend through the flexible rod, and that the microsystem could be in any position other than attached or otherwise fixed to the terminal end of the flexible rod.

It is also worthy of note that in Pompidou et al., the rigid microsystem (on which antibodies are arrayed) and the flexible rod are two distinct components, each having distinct characteristics. There is no insinuation that this could be made from one component (a fiber such as a flexible wire), as the contrasting characteristics (rigid versus flexible) would not be found in a single unified component such as the fiber of the instant invention.

4.1.3 The Rigid Support is Not Comparable to the Fibre Holding Region

On page 4 of the Action, the Examiner alleges that the rigid support described by Pompidou et al. is comparable to a fibre holding region, as defined in Claim 101. The applicant respectfully disagrees. Please note that the fibre holding region is one of two components that cooperate to form the positioning device itself. The purpose of the positioning device is stated in claim 101 as “for guiding the coated end [of the fiber] into position within a blood vessel. This characterization has no bearing on the purpose of the rigid support of Pompidou, which is merely the part of the microsystem that supports the antibodies. Looking more closely at the specified structure of the fibre holding region of claim 101, it is clear that the rigid support does not meet this criteria either. Specifically, the fibre holding region is “attached to” the fibre, and thus, is not the fibre itself. In the Examiner’s analogy where the microsystem is the equivalent of a fibre, then the rigid support (being a sub-component of the microsystem), could not be viewed as a separate component to which the microsystem is attached. Additionally, the fibre holding region is specified in claim 101 as movable with respect to the catheter. The Examiner provides no analogy as to how the rigid support itself is “movable” with respect to a

catheter (or any component viewed as a catheter equivalent). On the contrary, the rigid support is in fact fixed in position (the opposite of "movable") with respect to all aspects of the microsystem and the flexible rod, since it is fixed or attached to the terminal end of the flexible rod. The following passage from Pompidou et al. establishes that the rigid support is in such a fixed position:

> The results obtained on this work show that it is possible (i) *to fix on a rigid support (joined to a flexible rod) two antibodies* of different specificities (anti-Candida and anti-laminin), (ii) to sample corresponding analytes (Candida and laminin antigens), and (iii) to identify those analytes by antibodies labeled with biotin which is then revealed by a streptavidin-enzyme complex.

(Col 9, lines 23-29, emphasis added)

Because the Examiner's Obviousness objection was based on the assertion that the Pompidou et al. reference teaches *all* aspects recited in claim 1, (with the exception that the fiber is a flexible wire), it is believed that the above-noted rationale will assist the examiner in reviewing these objections and arriving at a revised conclusion, that indeed many important aspects of the invention as now claimed in claim 101 are absent from Pompidou et al., and are not solved by the additional teachings of Faxon et al.

4.1.4 The Faxon et al Reference Does Not Provide the Features Missing from Pompidou et al.

The Examiner states on page 4 that the only feature missing from Pompidou et al. is a flexible wire, and that such a flexible wire is provided by Faxon et al. The Applicant respectfully disagrees. First, that a number of aspects of claim 101 are missing from Pompidou et al. (for example, the positioning device itself (with both a catheter and a fibre holding region) is missing from the Pompidou et al. reference. However, this section will focus on the assertion that the Faxon et al. reference adequately provides a flexible wire to allow one skilled in the art to complete the teachings of Pompidou et al. to arrive at the invention as claimed in claim 101.

Briefly, the Faxon et al. reference describes a catheter fixed onto the terminal end of a guidewire. The guidewire itself is a typical type capable of inserting a catheter through a blood vessel. The following passage describes these features:

> Guidewire 45 is of the sort commonly used to direct a catheter through one or more bodily passageways such as blood vessels. More particularly, guidewire 45 is typically formed out of a strong flexible wire such that it can be passed through various bodily passageways to reach a remote site within a patient's body. Catheter 5 can then be loaded onto guidewire 45 and passed down the guidewire until it reaches the remote site. Movement of catheter 5 through these bodily passageways is facilitated by a blunt conical nose portion 50 (FIG. 1) which is fitted onto distal portion 30.

(Col 5, lines 37-44)

There is no mention in this document that such a guidewire should have a coated end at least partially coated with a polymeric extraction phase. In fact, this guidewire provides nothing more than a means of bringing into position the catheter which is disposed at the guidewire's terminal end. In this regard, the guidewire of Faxon et al. brings no more features than does the flexible rod of Pompidou et al., which had as its purpose bringing into position the microsystem which is disposed at its terminal end. The guidewire of Faxon et al. does not have any coating at its terminal end, but merely a catheter fixed thereon. In this way, the guidewire is not parallel to the fibre of claim 101 as it is not coated, nor is there any suggestion in Faxon et al. that it could be coated with an extraction phase. Such a terminal coating would be unlikely to succeed, given that a catheter is fixed at the terminal end of the guidewire. While the guidewire (and the flexible rod of Pompidou et al., for that matter) is flexible, it has no potential to bear the recited features of the fibre (or flexible wire) recited in claim 101, of possessing possess a coated end bearing a polymeric extraction phase.

4.2 Prima Facie Obviousness Has not Been Established

According to MPEP 2143, the three basic criteria for establishing *prima facie* obviousness are 1) suggestion or motivation in the references themselves or generally that the references be modified to combine the teachings; 2) reasonable expectation of success; 3) a teaching or suggestion that the combination be made, and the expectation of success must both be found in the prior art (not in the Applicants' disclosure). These criteria are referred to herein as the first criterion, the second criterion, and the third criterion. Further, in this discussion, it will be shown that the references are from unrelated art areas and are thus inappropriate to combine.

4.2.1 There is No Suggestion that the References be Modified to Combine the Teachings

The Pompidou et al. reference incorporates a "flexible rod" to position the microsystem. The inventors do not pine for some means by which the microsystem can be brought into position, there is no suggestion that the addition of guidewire could be of any benefit to the device described. In fact, a guidewire would merely provide a duplicate part, similar to the role of the flexible rod. Further, there is no suggestion that the rigid support on which antibodies are arrayed should instead be *replaced* by a guidewire. Indeed, the Pompidou et al. reference describes the need for a support to be rigid, and provides no alternative to a rigid support as a component of the microsystem.

The Faxon et al. reference does not suggest that the guidewire could be modified so as to provide a coated end for any reason. To the contrary, the purpose of the Faxon et al. device is to allow delivery of a catheter from which can extend needles to puncture a blood vessel in order to locally deliver a medicinally advantageous substance. It did not occur to Faxon et al. to coat the end of the guidewire with any type of substance, much less an extraction phase coating. There is no suggestion that the guidewire serve a dual purpose, or be used for any other reason than to guide a catheter into position.

4.2.2. There is no Reasonable Expectation of Success, Should the Teachings Be Combined

If the device of Pompidou et al. was modified to incorporate the guidewire of Faxon et al., the end result would not be the device as taught in claim 101. If the guidewire was simply added to the device of Pompidou et al., the result would be a microsystem to which both a guidewire and a flexible rod would be attached. Thus, the wire and rod would serve a redundant purpose, and no benefit would be realized. If the guidewire was used to guide the microsystem and flexible rod into place (as is its purpose in guiding the catheter into place), it would still not remedy the shortcoming that neither the rod nor the guidewire is coated with an extraction phase. If the guidewire was used to *replace* the flexible rod, it would still require a microsystem of the type described by Pompidou et al. to be affixed to its terminal end in order for the device to function. If the guidewire was used in place of the microsystem *per se*, the device would still would produce the successful result of being a single component. Instead, it

would still be a guidewire attached to a flexible rod. Claim 101 clearly stipulates that it is the fibre itself that terminates in a coated end, and that this *same* fibre extends through the catheter component of the positioning device.

If the device of Faxon et al. was modified to incorporate features of Pompidou et al., the end result would not be a catheter capable of piercing the wall of a blood vessel, which would have arrays of antibodies fixed onto the terminal end, either of the guidewire or of the catheter. Neither of these possible outcomes would reflect the device as taught in claim 101.

No combination of these two documents would allow a person skilled in the art to arrive at the successful outcome of having the fibre itself bear an extraction phase coating.

4.2.3. There is No Teaching Within Either Document That the Combination Is Warranted or Would be Successful

There is no statement within either the Pompidou et al. or the Faxon et al. document referring to possible modifications that would warrant replacement of the flexible rod, microsystem, rigid support, or guidewire with a single unified fibre as it is described in claim 101. None of the documents considers this option because in both devices, the terminal functional component is a physically discrete component (for Faxon et al., the catheter; for Pompidou et al., the microsystem) formed of a completely different material than the remaining components of the device. There is no teaching or suggestion in either document along the lines of: "there is a benefit in forming the functional end and the guidewire/flexible rod as one unified component" or "this device would benefit from the simplicity of combining the microsystem/catheter together with the flexible rod/guidewire". The absence of such a realization in either document illustrates that the combined teachings would not have been viewed as beneficial or successful. The additional modification required to both documents to arrive at a device where a flexible wire is coated with an extraction phase is not suggested in either document.

4.2.4. The References are from Unrelated Art and Are Inappropriate to Combine

The references come from disparate art, and are not appropriate to combine. A person skilled in the art, who may be looking in such classifications as the Pompidou et al. invention falls into (International class C12M 1/34 or major U.S. classification 435) would not think to look within

art in International class A61M 29/00 or major U.S. class 604. Not only does the classification of these devices illustrate the disparity, but the Pompidou device primarily is intended for in situ analysis, whereas the Faxon et al. device is intended for use with patients requiring local injection of drugs post angioplasty. The Faxon et al. device is intended for injection of a substance into a blood vessel wall, which neither the Pompidou et al. device or the device as claimed in claim 101 would permit. The Faxon et al. device is primarily intended for the use of cardiac surgeons and the like, whereas the Pompidou et al. device is intended primarily for analytical purposes. Each of the examples in Pompidou et al. relate to antibodies bound to the microsystem for detection of an antigen in the vicinity of the microsystem.

4.3. Obviousness Objection raised to Claims 102, 103, 106, 109 and 119 (Includes New Claims 120 and 121)

In the Rejection of claims 102, 103, 106, 109 and 119, the Examiner has combined the teachings of three references: Pompidou et al., Faxon et al. and Gourley et al. For reasons stated above in Sections 4.1 and 4.2, it is believed that the initial combination of the Pompidou et al. and Faxon et al. references was improperly applied, based on a misunderstanding of the components of claim 101, from which these claims depend. Thus, the addition of the third reference to the obviousness objection still does not provide the missing components that would allow a skilled reader to arrive at the device as claimed in claims 102, 103, 106, 109, 119, or new claims 120 and 121. The above rationale as it relates to claim 101 is incorporated into the arguments in support of these claims, with extra distinctions provided as follows.

Gourley et al. does not teach the limitations found in claim 101 from which these claims depend (for example, that the device requires fibre with a coated end) but further, Gourley in fact specifies that the apparatus must be “substantially rigid” Thus, the combination of Pompidou et al. and Gourley et al. do not render these claims obvious. There is no mention in Gourley et a., that the “sensing element” be coated on a flexible wire. The term “wire” is not used anywhere in the document. In the examples, a glass sleeve is used to surround the distal portion of an optical fibre. While various polymers or resins may be used to overcoat components of the device of Gourley et al., this does not permit a skilled reader to overcome

the deficiencies found in the Pompidou et al. and Faxon et al. references and arrive at the device now claimed in claims 102, 103, 106, 109, 119, 120 and 121.

If the Examiner persists in this objection, it is respectfully requested that all claims be assessed for the basis of their additional subject matter within the applied reference. For example, claim 103 now stipulates that the biocompatible protection layer comprises polypyrrole or derivatised cellulose, neither of which is mentioned in the Gourley at al. reference. Gourley et al. does not specify that a plurality of fibers (or even a plurality of sensors) could be incorporated into one device for positioning in separate locations in an animal or animal tissue, which is the subject of claim 109. The Examiner's reasoning that Gourley somehow insinuates multiple component detection could be brought about with multiple fibers (or sensors) incorporated into a single device is illogical and unsupported by any passage in the Gourley et al. reference. With respect to claim 119, there is no implication in Gourley et al. that multiple sensors (much less fibers) be positioned at the same location within a tissue. The examiner has not managed to locate a single passage in Gourley et al. that reflects this limitation recited in claim 119, and yet claim 119 was rejected out-of-hand without any attempt at such analysis. The subject matter of new claims 120 and 121 should be found as inventive over this combination of references, since neither Gourley et al., Pompidou et al., nor Faxon et al. recites the specific components of an extraction phase as now found in claims 120 and 121 in any way that could lead a skilled reader to the invention as claimed in these claims.

4.4 Obviousness Objection Raised to Claim 104

In the Rejection of claim 104, the Examiner has combined the teachings of three references: Pompidou et al, Faxon et al. and Colburn et al. For reasons stated above in Sections 4.1 and 4.2, it is believed that the initial combination of the Pompidou et al. and Faxon et al. references was improperly applied, based on a misunderstanding of the components of claim 101, from which this claim depends. Thus, the addition of the third reference to the obviousness objection still does not provide the missing components that would allow a skilled reader to arrive at the device as claimed in claim 104. The above rationale as it relates to claim 101 is incorporated into the arguments in support of this claim, with extra distinctions provided as follows.

Colburn et al. does not teach the limitations found in claim 104, it is merely a reference that relates to the MALDI. There is no reference to the use of a MALDI-TOFMS matrix on an SPME sampling device of any kind in the Colburn et al. reference. While the application of MALDI is common, the format of SPME-MALDI is unique since it incorporates the extraction phase, among other distinctions. There is nothing in this document to direct the skilled reader to include a matrix for MALDI-TOFMS analysis into an extraction phase coating, and to proceed to coat the end of a flexible wire with it.

4.5. Obviousness Objection Raised to Claim 105

In the Rejection of claim 105, the Examiner has combined the teachings of three references: Pompidou et al, Faxon et al. and Riviere et al. For reasons stated above in Sections 4.1 and 4.2, it is believed that the initial combination of the Pompidou et al. and Faxon et al. references was improperly applied, based on a misunderstanding of the components of claim 101, from which this claim depends. Thus, the addition of the third reference to the obviousness objection still does not provide the missing components that would allow a skilled reader to arrive at the device as claimed in claim 105. The above rationale as it relates to claim 101 is incorporated into the arguments in support of this claim, with extra distinctions provided as follows.

The use of calibration standards to spike a sample is common. The inclusion of the calibrant *within the extraction phase* as claimed in claim 105 is not the same as spiking a sample with a calibrant. The embodiment claimed in claim 105 specifies that the calibrant is *contained within* the extraction phase. This is an important point of novelty and inventiveness that the Examiner has overlooked. Riviere et al. place the calibrant into the system under investigation (via “spiking” of the investigated system). In a biological system where the device is intended for placement into a blood vessel, this would be the equivalent of injecting a calibrant into the blood stream, NOT the same as placement of a calibrant into the extraction phase coated onto a fibre that is then placed into the blood stream. In the former instance, the calibrant would rapidly circulate around the bloodstream of the system under investigation, and would become dilute at the site of sampling and/or the site of injection. This dilution effect would render useless the meaning of the calibrant, unless the entire bloodstream of the animal under

investigation was to be allowed to equilibrate with a constant level of calibrant. By way of contrast, the approach to calibration as recited in claim 105 is compatible with in-vivo monitoring since the calibrant itself primarily remains intact within the extraction phase, or allows only small amount of calibrant to possibly enter the blood stream or investigated tissue. This avoids the problem of contamination of the whole investigated system as in a typical "spiking" scenario.

The specific passages referred to by the Examiner at paragraphs 0167-0170 may have been misunderstood by the Examiner, and are clearly not equivalent to the inclusion of a calibrant in the extraction phase as in claim 105. The Examiner has failed to realize that the calibration compounds listed in these paragraphs are NOT coated onto fibers, are NOT included in any type of extraction phase, and are NOT exposed to a sample. These calibration standards are simply run concurrently with samples. The Applicant has concerns that the Examiner has taken the phrase "descriptor matrix" as used in [0167] out of context to mean that such calibrants were spiked into a coating. On the contrary, the "descriptor matrix" refers to the matrix of *values* that each calibrant molecule can be found at, used for statistical purposes in the comparative matrix of calibrant samples that were run. The calibrant samples were run *separately* from analysis of actual sample coatings, and only for the purpose of ensuring accurate calibration. There is no statement anywhere in Riviere et al. that any of these standards are doped into an extraction coating to be coated on the end of a fibre. Should the Examiner persist in this objection, she is invited to locate a passage that indicates, as does claim 105, that the *extraction phase itself* contains a calibrant.

4.6. Obviousness Objection Raised to Claims 107 and 118

In the Rejection of claims 107 and 118, the Examiner has combined the teachings of three references: Pompidou et al, Faxon et al. and Pawliszyn. For reasons stated above in Sections 4.1 and 4.2, it is believed that the initial combination of the Pompidou et al. and Faxon et al. references was improperly applied, based on a misunderstanding of the components of claim 101, from which these claims depend. Thus, the addition of the third reference to the obviousness objection still does not provide the missing components that would allow a skilled reader to arrive at the device as claimed in claims 107 and 118. The above rationale as it

relates to claim 101 is incorporated into the arguments in support of these claims. Pawliszyn does not provide the deficiencies missing from the Pompidou et al. and Faxon et al. references, and does not make any reference to indicate the possible use of a catheter, which is clearly required in claim 101, from which these claims depend. The catheter is again mentioned in claim 118, and thus it is not appropriate to use the Pawliszyn reference to form an obviousness rejection where the use of a catheter is required. The Examiner is thus requested to withdraw the objection.

5. Conclusion

It is requested that the Examiner reconsider the objection raised to the claims in view of the above-noted arguments, and withdraw the obviousness objection on this basis.

6. RCE, 1-Month Extension of Time, and Fees

Applicant submits simultaneously under separate cover a Request for Continued Examination (RCE), the requisite RCE fee, and the fee for a 1-month extension of time. The Applicant believes that no additional fee is due with this submission, but nevertheless authorizes the Commissioner to debit any required fee from or credit any overpayment to Deposit Account No. 501593, in the name of Borden Ladner Gervais LLP.

It is submitted that this application is in condition for allowance. Early and favorable reconsideration is respectfully requested.

Respectfully submitted,

Janusz B. PAWLISZYN

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